REMARKS/ARGUMENTS

The Pending Claims

Claims 1-17 are currently pending and are directed to a method of treating an intra-organellar acidification of intracellular organelles by the inhibition of vacuolar-type (H+)-ATPase.

Summary of the Office Action

Claims 1-7 and 12-17 stand rejected under 35 U.S.C. § 103(a) as obvious over McKee et al. (*J. Org. Chem.*, 63: 7805-7810 (October 2, 1998)) in view of Oku et al. (WO 99/21835) and Simon et al. (U.S. Patent Publication No. 2002/0042079). Claims 8-11 have been rejected under 35 U.S.C. § 103(a) as obvious over McKee et al. in view of Oku et al. and Simon et al. and further in view of Holt et al. (WO 93/18652) and Yamamoto et al. (*Cell Struct. Funct.* 23: 33-42 (1998)). Reconsideration of the pending claims is respectfully requested.

Discussion of the Obviousness Rejections

McKee et al., Oku et al., and Simon et al.

Claims 1-7 and 12-17 are rejected as obvious over McKee et al. in view of Oku et al. and Simon et al. The Office Action contends that McKee et al. discloses lobatamides A-D as having anti-tumor activity, while conceding that McKee et al. does not disclose the administration of apicularen A or B, the claimed amounts, or treatment of intra-organellar acidification of intracellular organelles. The Office Action asserts that it would have been obvious to use the claimed compounds in a method of treating cancer because McKee et al. describes the cytotoxicity of lobatamides A-D. The Office Action further contends that while other pathways are possible for the treatment of cancers, administration of the compounds disclosed by McKee et al. would "obviously meet the claims" because Oku et al. teaches that it is known in the art to treat cancers by inhibiting vacuolar-type (H+)-ATPase and Simon et al. teaches that it is known in the art to enhance the treatment of cancer by reducing acidification within organelles. The Office Action concludes the pending claims would have been obvious "because a claim for the administration of the same compound to the same

population is not rendered patentable by the discovery of a new mechanism by which the treatment works." This rejection is respectfully traversed.

McKee et al. discloses the structures of Lobatamides A-F (i.e., compounds **1-6**). Lobatamides A-D (compounds **1-4**) were tested for cytotoxicity using the National Cancer Institute's (NCI) human tumor 60 cell-line screen. Although the compounds were found to be cytotoxic, their profiles differed from other members of the NCI's standard agents database (abstract); p. 7809. As a result, McKee et al. concluded that the compounds appear to comprise a new mechanistic class, however, no details are provided regarding the actual mechanism. The mere disclosure in McKee et al. of anticancer activity in connection with the recited compounds does not render obvious the therapeutic inhibition of vacuolar-type (H+)-ATPase. The mere fact that an agent may be cytotoxic to cancer cells does not necessarily mean that the mechanism by which the compound is cytotoxic is by the inhibition of vacuolar-type (H+)-ATPase, that the compound is able to inhibit vacuolar-type (H+)-ATPase or that the compound can be used to treat intra-organellar acidification of intracellular organelles by the inhibition of vacuolar-type (H+)-ATPase. Moreover, while treatment of cancer is one possible result of inhibiting vacuolar-type (H+)-ATPase, the two are not mutually inclusive. It is well-known that inhibition of (H+)-ATPase can lead to treatment of many disease states other than cancer (e.g., urinary acidification, osteoporosis, and angiogenesis; see specification at, for example, page 2, line 7, through page 3, line 6 and page 20, line 17, through page 21, line 18). Also, cancer may be treated by inhibiting pathways other than (H+)-ATPase, such as inhibition of ras or estrogen receptor signaling (see, for example, Bredel et al., *Neurosurgery*, 43(1): 131-132 (1998), and Shen et al., *Oncol. Res.*, 10(6): 325-331 (1998), abstracts enclosed). Further, the Office Action acknowledges that McKee et al. do not teach "the administration of the apicularen A or B, the claimed amounts or the treatment of intra-organellar acidification of intracellular organelles, specifically."

Oku et al. and Simon et al. do not remedy the deficiencies of McKee et al. Oku et al. describes novel quinoline derivatives as (H+)-ATPase inhibitors. Oku et al. further discloses that since the compounds inhibit vacuolar-type (H+)-ATPase, they are useful for the prevention and/or treatment of several disorders, including malignant tumors (page 15,

line 30, through page 16, line 21). However, the quinoline derivatives, i.e., compounds of formula (I), are not structurally related to the compounds recited in claims 1-17.

Simon et al. relates to a method for the monitoring of the likelihood or onset of multidrug resistance in mammals and the identification and monitoring of agents useful for minimizing multidrug resistance, particularly with respect to the treatment of cancer (paragraph [0073]). In addition, Simon et al. describes that chemotherapeutic compounds that reduce organelle acidification should reverse drug resistance because of enhanced sensitivity of tumor cells (paragraph [0187]). In this regard, Simon et al. discloses the chemotherapeutic classes: anthracyclines and vinca alkaloids, which are very structurally different than the compounds recited in claims 1-17.

Oku et al. and Simon et al. do not teach or suggest any compounds that even remotely resemble the compounds claimed in the pending claims (i.e., the compounds of formulae (I) and (IF)). Since McKee et al. does not hint at or even suggest any type of mechanism by which the McKee et al. compounds act and the McKee et al. compounds are so structurally different from the compounds disclosed in Oku et al. and Simon et al., absent the teachings of the present application and the impermissible use of hindsight, one of ordinary skill in the art would not be lead to Oku et al. and Simon et al. to remedy the deficiencies in McKee et al., namely, the administration of the claimed compounds to treat an intra-organellar acidification of intracellular organelles by the inhibition of vacuolar-type (H+)-ATPase. The rejection is thus unsupported factually and legally. "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability, this amounts to nothing more than impermissible hindsight." *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617. (Fed. Cir. 1999). Thus, one having ordinary skill in the art would not have been motivated to somehow combine the diverse teachings of the cited references and somehow arrive at the presently claimed method.

Indeed, even if one skilled in the art were to have selectively chosen the disclosures of McKee et al., Oku et al., and Simon et al., there is no suggestion in the references to combine their teachings in such a way as to arrive at a method of treating an intra-organellar acidification of intracellular organelles by the inhibition of vacuolar-type (H+)-ATPase with

the compounds described in the pending claims. There is nothing in Oku et al. and Simon et al. to suggest that intra-organellar acidification can be treated by inhibiting vacuolar-type (H+)-ATPase. Oku et al. discloses that quinoline derivatives that inhibit vacuolar-type (H+)-ATPase are useful to treat cancer, but says nothing about treating intra-organellar acidification. Simon et al. describes that chemotherapeutic compounds that reduce organelle acidification can be used to treat cancer, but says nothing about inhibiting vacuolar-type (H+)-ATPase. McKee et al. does not teach or suggest the concepts of inhibiting vacuolar-type (H+)-ATPase or treating intra-organellar acidification. As a result, there simply is no nexus between the two concepts in any of the cited references. Thus, even with the combined disclosures of McKee et al., Oku et al., and Simon et al., one of ordinary skill in the art would not have arrived at a method of treating an intra-organellar acidification of intracellular organelles by the inhibition of vacuolar-type (H+)-ATPase, as defined by pending claims 1-17.

Further, McKee et al. does not recite any compounds that structurally resemble the compound of formula (IF), as recited in claims 6 and 7. In particular, no compound in McKee et al. has a tricyclic structure, let alone a tricyclic structure comprising a 10-membered ring fused to two 6-membered rings. Accordingly, the compound of formula (IF) is not an obvious structural variation of the compounds disclosed in McKee et al. Oku et al. and Simon et al. also do not describe the compound of formula (IF). Thus, the combination of cited references does not disclose all of the elements of claims 6 and 7, and claims 6 and 7 are, therefore, independently patentable over the cited references.

In view of the foregoing, claims 1-17 and claims 6-7 would not have been obvious to one of ordinary skill in the art in view of McKee et al. either alone or in combination with Oku et al. and Simon et al. As such, the obviousness rejection based on these references should be withdrawn.

McKee et al., Oku et al., Simon et al., Holt et al., and Yamamoto et al.

Claims 8-11 have been rejected as allegedly obvious over McKee et al. in view of Oku et al. and Simon et al. and further in view of Holt et al. and Yamamoto et al. The disclosures of McKee et al., Oku et al., and Simon et al. have been discussed above. Holt et al. purportedly discloses the administration of bafilomycins, which inhibit

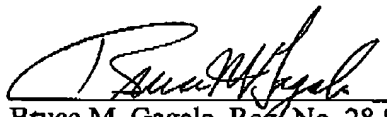
(H+)-ATPase, for the treatment of cancer. Yamamoto et al. allegedly discloses the equivalent activities of bafilomycin A_1 and concanamycins regarding vacuolar (H+)-ATPase inhibition.

As discussed above, the disclosure of McKee et al. alone or in combination with Oku et al. and Simon et al. does not render the invention defined by claims 8-11 obvious. Holt et al. and Yamamoto et al. merely describe another class of compounds which exhibit (H+)-ATPase inhibition for the treatment of cancer, but which bear no relationship to the compounds used in the claimed method. Thus, even with the added disclosures of Holt et al. and Yamamoto et al., the cited references do not teach or suggest a method of treating an intra-organellar acidification of intracellular organelles by the inhibition of vacuolar-type (H+)-ATPase with the compounds described in the pending claims. As such, claims 8-11 would not have been obvious to one skilled in the art in view of these references, and the rejection should be withdrawn.

Conclusion

Applicants respectfully submit that the application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



Bruce M. Gagala, Reg. No. 28,844
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson Avenue
Chicago, Illinois 60601-6780
(312) 616-5600 (telephone)
(312) 616-5700 (facsimile)

Date: February 6, 2006

1: Neurosurgery. 1998 Jul;43(1):124-31; discussion 131-2.

Inhibition of Ras and related G-proteins as a therapeutic strategy for blocking malignant glioma growth.

Bredel M, Pollack IF, Freund JM, Hamilton AD, Sebti SM.

Department of Neurosurgery, University of Pittsburgh Cancer Institute Brain Tumor Center, University of Pittsburgh School of Medicine and the Children's Hospital of Pittsburgh, Pennsylvania 15213, USA.

OBJECTIVE: Preliminary studies have demonstrated that the Ras family and related guanosine 5'-triphosphate-dependent proteins (G-proteins) are overactivated in malignant gliomas and may function as indirect mediators of glial transformation initiated by deregulated upstream signaling elements. We postulated that inhibiting the activation of such proteins might represent a promising strategy for blocking the aberrant proliferation of these tumors. METHODS AND RESULTS: Accordingly, we examined the therapeutic efficacy against malignant glioma cells in vitro of a series of selective peptidomimetic inhibitors of farnesylation (FTI-277) and geranylgeranylation (GGTI-286 and GGTI-298), which are critical steps in the post-translational processing (prenylation) of these proteins. We first defined concentration-response relationships for each of these agents, using MTS-based cell proliferation assays in the established malignant glioma cell lines U-87 and LN-Z308 and the low-passage malignant glioma cell line SG-388. FTI-277, GGTI-286, and GGTI-298 each produced a striking concentration-dependent antiproliferative effect on the glioma cell lines, with the median effective dose ranging from 2.5 to 15.5 micromol/L. We then assessed the effect of prenylation inhibition on cell viability using clonogenic growth assays. This demonstrated a steady drop in the number of colonies with increasing drug concentrations for all three inhibitors. Third, we examined whether the cytotoxic effects of one of these inhibitors (GGTI-298) were associated with the induction of apoptosis using a terminal transferase-catalyzed in situ end-labeling technique. This approach showed a time-dependent increase in apoptotic cell numbers, which correlated with a progressive decrease in the percentage of cells that were viable as assessed by trypan blue exclusion. CONCLUSION: Our studies demonstrated that FTI-277, GGTI-286, and GGTI-298 each yielded significant antiproliferative effects in human malignant glioma cells in vitro at low micromolar concentrations, which have been achievable in vivo without major systemic toxicity. Extended periods of drug treatment produced cytotoxicity in the tumor cells, which correlated with the induction of apoptosis. We conclude that inhibition of Ras and related G-proteins offers a promising approach for blocking glioma proliferation that justifies further investigation in vivo.

PMID: 9657198 [PubMed - indexed for MEDLINE]

1: Oncol Res. 1998;10(6):325-31. Related Articles, Links

Tamoxifen downregulates signal transduction and is synergistic with tiazofurin in human breast carcinoma MDA-MB-435 cells.

Shen F, Weber G.

Laboratory for Experimental Oncology, Indiana University School of Medicine, Indianapolis 46202-5119, USA.

Breast carcinoma is a leading cause of cancer death in women in the US. Tamoxifen (TAM), an antiestrogen, is used as a chemopreventive and chemotherapeutic compound against human breast carcinoma. Tiazofurin (TR), an oncolytic C-nucleoside, inhibits IMP dehydrogenase activity, decreases cellular GTP pools, and downregulates ras gene expression. MDA-MB-435 cells are estrogen receptor negative human breast carcinoma cells that have elevated signal transduction activity. Because TR and TAM decrease signal transduction enzyme activity and inositol 1,4,5-trisphosphate (IP3) concentration via different mechanisms, we tested the hypothesis that the two compounds may be synergistic in human breast carcinoma cells. In MDA-MB-435 cells in growth inhibition assay, the IC50s for TR and TAM were (mean +/- SE) 17 +/- 1.2 and 12 +/- 1.1 microM; in clonogenic assays they were 4 +/- 0.3 and 0.7 +/- 0.3 microM, respectively. When TR was added to MDA-MB-435 cells, followed 12 h later by TAM, synergism was observed in growth inhibition and clonogenic assays and in the reduction of IP3 concentration. The latter may explain, at least in part, the synergistic action of TR and TAM in these cells. The synergistic action of TR and TAM may have implication in the clinical treatment of human breast carcinoma.

PMID: 9848103 [PubMed - indexed for MEDLINE]